Eur J Clin Pharmacol (2009) 65:999–1006
DOI 10.1007/s00228-009-0683-y

PHARMACOKINETICS AND DISPOSITION

Effect of ritonavir on the pharmacokinetics of the benzimidazoles albendazole and mebendazole: an interaction study in healthy volunteers

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Received: 9 January 2009 / Accepted: 3 June 2009 / Published online: 27 June 2009

Abstract
Background Benzimidazoles are often used concomitantly with protease inhibitors in patients with helminthic disease and HIV infection. Low bioavailability and extensive first-pass metabolism make benzimidazoles prone to pharmacokinetic drug interactions. The aim of the present study was to investigate potential drug interactions between the benzimidazoles albendazole and mebendazole and the potent CYP3A4 inhibitor ritonavir.
Methods Sixteen healthy volunteers were administered a single oral dose of 1,000 mg mebendazole or 400 mg albendazole ($2\times n=8$). AUC, C_{max}, and $t_{1/2}$ of mebendazole, albendazole, and albendazole sulfoxide were studied in absence and after short-term (2 doses) and long-term (8 days) treatment with ritonavir 200 mg bid.
Results Pharmacokinetic parameters of albendazole and mebendazole were not changed by short-term administration of ritonavir. However, long-term administration of ritonavir resulted in significant changes in albendazole and mebendazole disposition, with a significant decrease in $AUC_{0\text{-}24}$ (27 and 43% of baseline for albendazole and mebendazole, respectively) and C_{max} (26 and 41% of baseline, respectively).
Conclusion The $AUC_{0\text{-}24}$ of benzimidazoles decreased after long-term use of ritonavir, while no changes in pharmacokinetic profiles were observed under short-term administration. These findings might help to optimize benzimidazole efficacy when used in combination with protease inhibitors.

Keywords Benzimidazoles · Albendazole · Mebendazole · Ritonavir · Drug interaction

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Introduction

Albendazole and mebendazole are benzimidazoles used for the therapy of various helminthic infections as well as for the treatment of hydatid disease (*Echinococcus granulosus*) and alveolar echinococcosis (*Echinococcus multilocularis)* [1]. The combination of benzimidazoles with anti-HIV medications such as protease inhibitors is increasingly used in developing countries, where both helminthic disease and HIV infection are endemic [2]. While HIV therapy is not affected by co-administration of benzimidazoles [2], no data are so far available on the effect of protease inhibitors on antiparasitic treatment. However, low bioavailability and extensive first-pass metabolism make benzimidazoles especially prone to pharmacokinetic drug interactions, and dose-related toxicity could therefore arise in combination with potent

inhibitors of benzimidazole metabolism. In line with these concerns, a metabolic drug interaction was recently suggested as the underlying pathophysiological mechanism of a case of severe dose-related hematological toxicity described under comedication of albendazole and mebendazole with the protease inhibitors ritonavir and nelfinavir [3].

After oral administration, albendazole and mebendazole are poorly absorbed in the intestinal tract, mainly due to limited solubility [4]. Furthermore, benzimidazoles undergo extensive intestinal and hepatic bioconversion, adding to the low systemic exposures with these compounds [5, 6]. In case of albendazole, different cytochrome P450 enzymes (CYP) and the flavine-containing monooxygenase (FMO) system seem to be responsible for intestinal and hepatic sulfoxidation of the parent compound to albendazole sulfoxide [6, 7], while CYP1A2 is involved in sulfonidation [8]. Formation of albendazole sulfoxide is stereoselective with CYP3A4 being the key player in the formation of (-)-albendazole sulfoxide, whereas formation of (+)-albendazole sulfoxide is mediated by the FMO system [7]. In line with these observations, co-administration of CYP3A4 inhibitors such as cyclosporine or ketoconazole was associated with increased albendazole plasma levels in different animal models, which was interpreted as a result of inhibited intestinal elimination of albendazole [9]. Furthermore, the non-selective cytochrome P450 inhibitor clotrimazole and the FMO inhibitor methimazole significantly inhibited albendazole metabolism in rat liver microsomes [7]. In contrast, only few data are available on specific enzymes involved in the metabolism of mebendazole. Metabolites isolated from feces and urine as well as results of the aminopyrine breath test suggest the involvement of a keton reductase and different CYP isoforms [10, 11]. Furthermore, interaction data in healthy volunteers indicate that the non-specific cytochrome P450 (CYP) inhibitor cimetidine significantly increases mebendazole plasma levels [10, 12], pointing towards an involvement of cytochrome P450 enzymes in mebendazole metabolism.

The protease inhibitor ritonavir is among the most potent inhibitors of the CYP3A system [13]. Consequently, interaction of protease inhibitors with drugs that are cleared predominantly by CYP3A enzymes are profound and clinically significant [14]. It is still equivocal whether long-term administration of ritonavir may also lead to a certain induction of CYP3A enzymes [15]. However, studies both in healthy volunteers [16] and patients [17] do not support CYP3A4 induction.

Given the lack of systematic data on the disposition and interaction of benzimidazoles with protease inhibitors the aim of the present study was to investigate potential drug interactions between the benzimidazoles albendazole and mebendazole and ritonavir under single-dose and steady-state conditions. The protease inhibitor ritonavir was chosen as model inhibitor because of its anticipated use in combination with benzimidazoles and its reported association with dose-related toxicity of albendazole and mebendazole. Furthermore the effect of long-term administration of ritonavir on benzimidazole metabolism was investigated.

Methods

Patients and study design

After approval by the local ethics committee and written informed consent, 16 healthy, nonsmoking, HIV-negative male Caucasian volunteers were included in the study. All participants had to be healthy as confirmed by physical examination and routine laboratory screening of hematological and clinical-chemical parameters, including renal, hepatic, and pancreatic parameters. None of the participants took any regular medication, and all abstained from alcohol for the duration of the study. Because of possible gender-related differences in the pharmacokinetic profiles of albendazole metabolites [18], only male volunteers were included.

The study was performed at the Clinical Research Unit of the University Hospital Zürich. To minimize food-associated variability in absorption, study medication was administered after an overnight fast. Volunteers were given a single oral dose of 1,000 mg mebendazole (Vermox tablets 500 mg, Janssen-Cilag, Baar Switzerland) (n=8 individuals) or 400 mg albendazole (Zentel tablets, GlaxoSmithKline, Münchenbuchsee, Switzerland) (n=8 individuals). Mebendazole and albendazole were taken in the morning of three independent days (days 1, 8, and 15) with 100 ml water. Oral ritonavir 200 mg bid (Norvir 100 mg capsules, Abbott, Baar, Switzerland) was started in the evening of day 7 and was continued until the morning of day 15. Standardized breakfast and lunch were served after the 2-h and the 4-h blood samples.

Pharmacokinetic profiles of albendazole and mebendazole were performed on day 1 (baseline), day 8 (after 2 doses of ritonavir), and day 15 (long-term ritonavir). Blood samples for the analysis of albendazole and mebendazole were drawn from a venous line before and after 30 min and 1, 2, 3, 4, 6, 10, and 24 h after the benzimidazole administration. Ritonavir samples were taken once in the morning of day 8 and 15 for compliance control. All blood samples were immediately centrifuged at 4°C and the plasma stored at -20°C until further analysis.

Study participants were allowed to leave the trial unit on the evenings of day 1, 8, and 15 and returned for the '24-h sample on the following morning. On the last pharmacokinetic day (day 15), a liver, pancreatic, and renal panel was performed for safety reasons.

Analysis of albendazole and mebendazole

Plasma concentrations of albendazole, its active metabolite albendazole sulfoxide, mebendazole, and ritonavir were measured at the Institute of Clinical Chemistry, University Hospital Zurich. Albendazole, albendazole sulfoxide, and mebendazole with flubendazole as internal standard (IS) were determined by liquid chromatography tandem mass spectrometry with positive atmospheric pressure chemical ionization (LC-MS/MS). The different benzimidazoles were separated with reversed-phase chromatography using a gradient system of ammoniumformiate buffer pH 3, methanol, and acetonitrile. A 1-ml sample of plasma was extracted by solid-phase extraction using C18 columns. Elution was performed with 2 ml methanol containing 2.5% dimethyl sulfoxide. Quantitation was achieved using selected reaction monitoring (SRM) of the transitions of m/z 266→234 for albendazole, m/z 282→240 for albendazole sulfoxide, m/z 296→264 for mebendazole, and m/z 314→282 for the IS.

The standard curves were plotted as the peak area ratio of the respective benzimidazole to the internal standard. To assess linearity, the best fit was determined by least square regression. The accuracy of the method was 103% for albendazole, 102% for albendazole sulfoxide, and 101% for mebendazole, respectively. The intra- and interday coefficients of variation were <10% for all analytes.

Pharmacokinetic analysis

Changes in albendazole and mebendazole pharmacokinetics were evaluated under concomitant short-term (day 8) and long-term (day 15) intake of ritonavir. The maximum plasma concentration (C_{max}) and the time of occurrence of C_{max} (T_{max}) were taken from concentration time curves. Plasma concentrations of albendazole, albendazole sulfoxide, and mebendazole were plotted semi-logarithmically against time, and the AUC was calculated by the trapezoidal rule for the periods from 0 to 24 h. The apparent terminal half-life ($t_{1/2}$) was estimated by non-compartmental analysis using the pharmacokinetic software WinNonlin Version 5.0. (Pharsight, Cary, NC).

Power calculation

The aim of this study was to compare pharmacokinetic profiles of albendazole and mebendazole under concomitant short-term and long-term administration of the CYP3A4 and P-glycoprotein inhibitor ritonavir. Changes in $AUC_{0\text{-}24}$ and C_{max} were chosen as primary endpoints. Sample size calculation was based upon the following considerations: (1) the extent of interindividual variability in albendazole pharmacokinetics in healthy volunteers [4], (2) the extent of interindividual variability of multiple-dose oral ritonavir pharmacokinetics in healthy volunteers [19], (3) the observed increase in simvastatin AUC in an interaction study with ritonavir [20], as simvastatin exhibits a bioavailability comparable to that of mebendazole and albendazole, and (4) the observed increase in mebendazole plasma concentrations under co-treatment with ritonavir in a single-case observation [3]. While the expected increase in C_{max} and AUC of benzimidazoles is about 20-fold under short-term use of ritonavir, the increase is expected to level off to about 4-fold under long-term use. Eight individuals per group are required to detect this 4-fold increase from baseline kinetics with a power of 80% and a significance level of 0.05.

Data analysis

Primary parameters for the assessment of an interaction were the $AUC_{0\text{-}24}$ and the C_{max} of the three analytes (multiplicative models applied), while T_{max} and $t_{1/2}$ were additionally investigated. The interaction was handled as a bioequivalence problem [21]. The effect of short-term and long-term administration of ritonavir on the pharmacokinetics of mebendazole, albendazole, and albendazole sulfoxide was evaluated. Point estimates and the corresponding 90% confidence intervals of the two geometric mean ratios of the pharmacokinetic parameters in the study periods with ritonavir over those without ritonavir were calculated. An interaction was accepted to be present if the 90% confidence interval around the geometric mean ratio was entirely outside the accepted reference range of 0.80-1.25.

Results

Study participants and safety

Sixteen healthy male volunteers were enrolled in this study, eight in the albendazole and eight in the mebendazole arm. The mean age of study participants was 31 years (range 20–46 years) and the mean weight was 73 kg (range 60–101 kg). All volunteers successfully completed the study. Two of the participants complained about slight diarrhea while taking ritonavir, which reversed without sequelae. No serious adverse events occurred.

Albendazole and mebendazole kinetics

Individual pharmacokinetic parameters showed high interindividual variability: individual albendazole and albendazole sulfoxide $AUC_{0\text{-}24}$ values differed by more

than 20-fold and mebendazole $AUC_{0\text{-}24}$ values differed more than 7-fold on the first pharmacokinetic day (Fig. 1a–c). Outliers with excessively high $AUC_{0\text{-}24}$ and C_{max} values were seen in single individuals (individual 3 for albendazole, due to double-peaked plasma concentration time curves, and individual 9 for mebendazole; data not shown). The pharmacokinetics of albendazole, its metabolite albendazole sulfoxide, and mebendazole were not significantly changed by the administration of short-term ritonavir as the 90% confidence interval of $AUC_{0\text{-}24}$ and C_{max} overlapped the bioequivalence criteria (0.80-1.25) (Table 1). Apart from individual 3 with a strong decrease in albendazole and albendazole sulfoxide AUC on the second PK-day after intake of two doses of ritonavir (Fig. 1b, c), only minimal changes in individual albendazole and albendazole sulfoxide $AUC_{0\text{-}24}$ values were seen in the remaining study participants. The trend toward a decrease in the $AUC_{0\text{-}24}$ mean value in the albendazole group on the second PK-day is probably due to the $AUC_{0\text{-}24}$ outliers on the first PK-day. In the mebendazole group, a trend towards an increase in mebendazole exposure after short-term intake of ritonavir was seen. Four of eight participants (individuals 10, 12, 15, and 16) had an increase in mebendazole exposure of 30–80%, while three individuals exhibited hardly any change in exposure, and in one individual $AUC_{0\text{-}24}$ decreased by 35%.

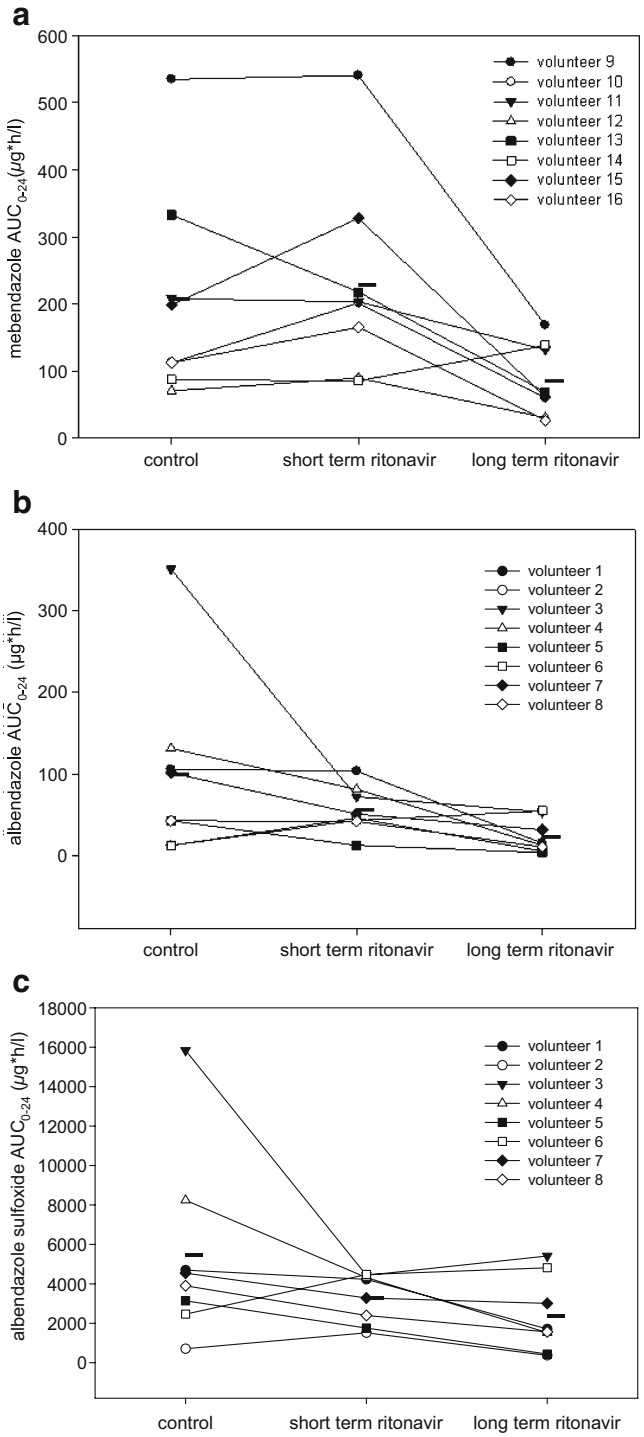

Fig. 1 Individual $AUC_{0\text{-}24}$ on different pharmacokinetic days of **a** mebendazole, **b** albendazole, and **c** albendazole sulfoxide. The *horizontal lines* represent mean values

Administration of ritonavir for 1 week, however, resulted in significant changes in albendazole and mebendazole disposition, with a significant decrease in $AUC_{0\text{-}24}$ and C_{max} compared to baseline values (Table 1 and Fig. 2a–c). Mebendazole $AUC_{0\text{-}24}$ and C_{max} were reduced to 0.43 and 0.41 (geometric mean ratio) of baseline values, respectively, while albendazole and albendazole sulfoxide $AUC_{0\text{-}24}$ and C_{max} were reduced to 0.27 and 0.26 and to 0.41 and 0.52, respectively. The confidence intervals of the geometric mean ratios were outside the bioequivalence criteria, so that an interaction had to be accepted as present. This was also true when geometric mean ratios were recalculated without the outliers for both groups, i.e., individual 3 for albendazole [GM ratios $AUC_{0\text{-}24}$:0.30 (0.14-0.60) and C_{max}: 0.26 (0.09-0.70)] and individual 9 for mebendazole [GM ratios $AUC_{0\text{-}24}$:0.45 (0.29-0.69) and C_{max}: 0.45 (0.28-0.72)]. Only the GM ratios for albendazole sulfoxide slightly overlapped the bioequivalence criteria for the AUC [GM ratios $AUC_{0\text{-}24}$:0.57 (0.34-0.95) and C_{max}: 0.43 (0.27-0.68)]. At the same time, T_{max} and the terminal half-life did not change significantly. In all individuals, ritonavir was detected in the plasma on the second and the third PK-day with concentrations ranging from 0.14 to 10 mg/l. In two individuals in the mebendazole group who complained about slight diarrhea between the second and the third PK-day, $AUC_{0\text{-}24}$ dropped by 70% on the third PK-day. A diminished absorption of mebendazole caused by increased intestinal activity can therefore not fully be excluded in these particular cases.

Table 1 Pharmacokinetic parameters of mebendazole, albendazole, and albendazole sulfoxide before and after short-term (two doses) and long-term (8 days) treatment with ritonavir in eight healthy volunteers

	Before ritonavir	Short-term ritonavir			Long-term ritonavir		
	Mean±SD[a]	Mean±SD[a]	Geometric mean (GM) ratio[b]	90% Confidence interval of GM ratios	Mean±SD[a]	Geometric mean (GM) ratio[b]	90% Confidence interval of GM ratios
Mebendazole							
AUC_{0-24} (μg·h/l)	207.2±157.6	228.9±147	1.17	0.81–1.70	85.9±53.2	0.43	0.30–0.62
C_{max} (μg/l)	31.0±26.0	36.0±22.8	1.18	0.79–1.80	11.5±6.2	0.41	0.27–0.63
T_{max} (h)	2.1±1	2.4±1.7			2.1±0.8		
Terminal $t_{1/2}$ (h)	7.4±2.2	9.3±3.5			10.6±8.6		
Albendazole							
AUC_{0-24} (μg·h/l)	100.1±110.8	56.6±28.1	0.83	0.42–1.61	23.6±20.7	0.27	0.14–0.52
C_{max} (μg/l)	15.3±10.3	16.0±9	1.24	0.52–2.95	4.9±5.2	0.26	0.11–0.62
T_{max} (h)	2.1±1.1	1.8±1.1			2.3±1.8		
Terminal $t_{1/2}$ (h)	10.2±10.2	10.1±7.3			17.3±15.5		
Albendazole sulfoxide							
AUC_{0-24} (μg·h/l)	5,441.3±4,725.2	3,299.8±1,249.8	0.77	0.50–1.20	2,354.0±1,896.6	0.41	0.26–0.65
C_{max} (μg/l)	453.9±398.7	273.3±119.6	0.79	0.50–1.26	230.9±151.4	0.52	0.32–0.83
T_{max} (h)	4.1±3.6	2.9±2.0			3.6±3.1		
Terminal $t_{1/2}$ (h)	17.3±13.6	13.2±5.6			8.9±4.6		

[a] Arithmetic mean

[b] Ratio of geometric means (GM) of values under short- or long-term ritonavir treatment to values before treatment with ritonavir

Discussion

In the present study we investigated the effect of short- and long-term administration of ritonavir on the disposition of the benzimidazoles albendazole and mebendazole in healthy volunteers. As expected from previous data on oral albendazole and mebendazole disposition [4, 12], high interindividual variability in bioavailability was seen. While single-dose administration of the potent CYP3A inhibitor ritonavir did not result in changes in albendazole and mebendazole plasma concentrations in most of the patients, long-term administration led to a significant decrease in benzimidazole systemic exposure.

Inhibition of albendazole and mebendazole metabolism under co-administration of ritonavir has been expected based upon the low oral bioavailability of these drugs and evidence for an important contribution of cytochrome P450 enzymes to in-vitro metabolism [22]. While the relative contribution of different CYP enzymes has not been identified for mebendazole, CYP3A seems to be one of the key players for albendazole biotransformation [7]. However, albendazole has been classified as a high-clearance drug, with hepatic metabolism being essentially flow-limited [22].

On the other hand, significant drug interaction after oral administration can still arise at the level of intestinal drug absorption, where metabolizing enzymes and transporter systems expressed in small intestinal enterocytes represent an important first presystemic barrier. Recent evidence points towards an involvement of the breast cancer resistance protein BCRP (ABCG2) in this process, while MDR1 P-glycoprotein, which could potentially be inhibited by ritonavir, is not involved in benzimidazole transport [23]. Overall, flow-limited hepatic metabolism and predominant intestinal clearance by BCRP would explain the observation that albendazole disposition is not affected by intake of two doses of ritonavir.

In contrast, ritonavir is an inducer of several phase I and phase II enzymes and transporters [24] in a dose-dependent manner. A 12% decrease in ritonavir exposure was already seen with doses of 400 mg daily, and exposure further decreased by 45% with ritonavir 1,000 mg/day [19]. An increase in cytochrome 2C9, 2C19, and 1A2 activity by ritonavir was shown in human hepatocytes [15] as well as under long-term treatment with lopinavir boosted with 200 mg ritonavir daily in healthy volunteers [16]. As CYP2C9 and CYP1A2 are involved in albendazole and albendazole sulfoxide metabolism [22], their induction by long-term ritonavir administration of 400 mg daily could explain a lower bioavailability of albendazole. Accordingly, a partial involvement of CYP2C and CYP1A2 enzymes in mebendazole metabolism could be postulated as an even more pronounced reduction in mebendazole was noted in our study. Induction of phase II enzymes could represent an

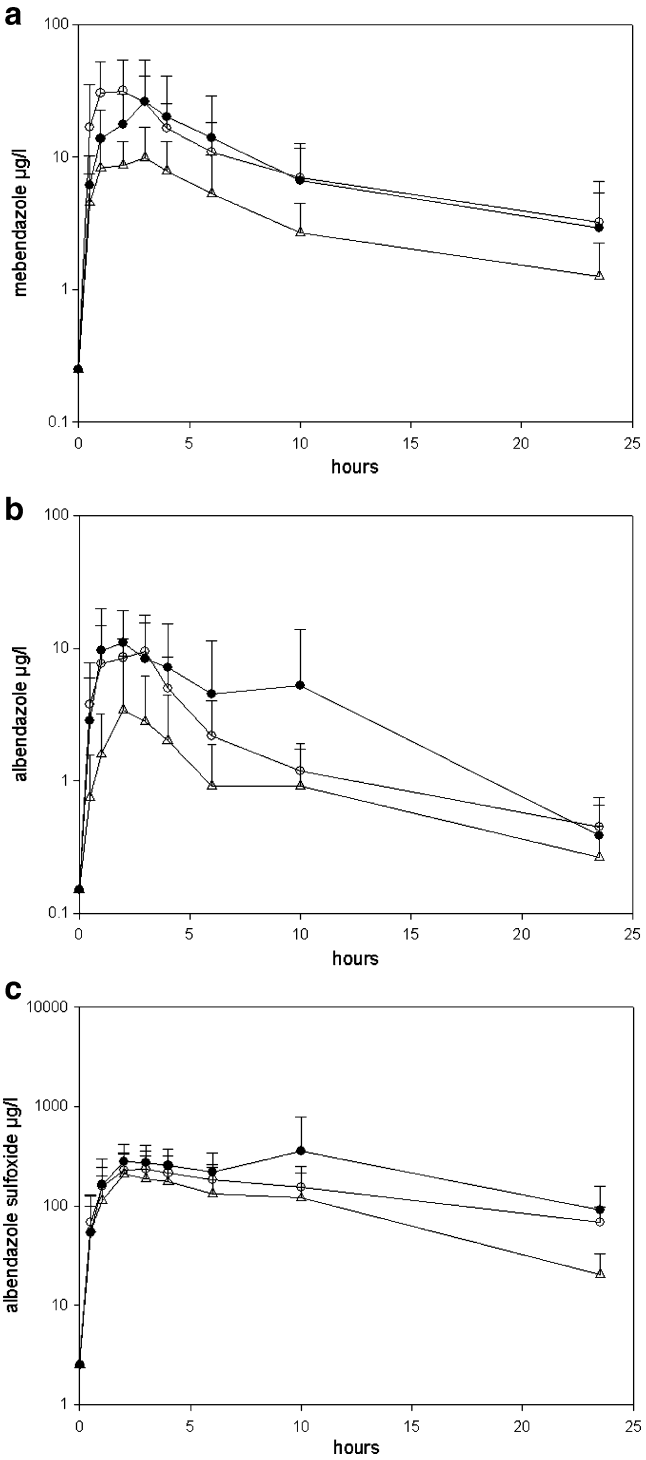

Fig. 2 Serum concentration time curves on different pharmacokinetic days of **a** mebendazole, **b** albendazole, and **c** albendazole sulfoxide. Baseline values (day 1) are represented by *black circles*, short-term ritonavir by *white circles*, and long-term ritonavir by *triangles*. *Error bars* represent standard deviation

alternative explanation as the CYP system is only partially involved and mebendazole conjugates are excreted as metabolites [11]. Ritonavir induces UDP-glucuronosyltransferase 1A1 (UGT1A1) in vitro [25], and plasma concentrations of substances mainly conjugated by UGT-like lamotrigine are markedly reduced by ritonavir co-administration [26].

Intraindividual variability due to poor and variable absorption of the low water-soluble drugs albendazole and mebendazole might also have contributed to the observed reduction in exposition. Albendazole and mebendazole absorption is increased by fatty meals [4], and a pH dependency has been postulated for albendazole absorption [27]. To evaluate the importance of variability in intestinal absorption on our findings, data were recalculated without the outliers with the highest AUC values in the albendazole group (individual 3) and the mebendazole group (individual 9). Even by excluding these individuals from our analysis, decrease in AUC and C_{max} for albendazole and mebendazole after long-term ritonavir administration still did not meet the bioequivalence criteria, pointing towards a mechanism other than differences in drug absorption to be responsible for our observations. The slight overlap with the bioequivalence criteria of the albendazole metabolite is unlikely to be primarily due to differences in intestinal absorption. Furthermore, as no differences in C_{max} and AUC values were observed between individuals with and without diarrhea, changes in gastrointestinal motility were not considered to be the main reason for the overall decrease in albendazole and albendazole sulfoxide AUC under long-term ritonavir intake.

Several conclusions can be drawn from this study: First, CYP3A and P-glycoprotein inhibition by ritonavir does not affect albendazole or mebendazole disposition, and there should be no concern about dose-related benzimidazole toxicity when using combination therapies with protease inhibitors. Furthermore, with some caution, these observations can be extrapolated to other drugs known to inhibit CYP3A or P-glycoprotein, which very probably can safely be co-administered in patients with helminthic disease. Second, as BCRP seems to be a determinant of intestinal elimination of albendazole metabolites, inhibition or induction of this efflux process might potentially result in drug interactions. However, the in-vivo significance of BCRP inhibition remains to be determined and seems to be insignificant in the case of ritonavir. Third, long-term use of this combination results in decreased exposure of albendazole and mebendazole and might therefore affect treatment efficacy. This effect is most probably not only due to a ritonavir-mediated induction of metabolizing enzymes or transporters but could be related to low intestinal absorption and changes in gastrointestinal function.

However, although our data help to mechanistically understand the effect of ritonavir on benzimidazole metabolism and transport, they do not reflect the clinical treatment reality of HIV-infected patients, where ritonavir is almost never given as the single protease inhibitor

but instead is given as part of a combination therapy. The effect of boosted protease inhibitor combinations such as lopinavir/ritonavir or atazanavir/ritonavir, which are components of standard drug regimens in HIV patients, on mebendazole and albendazole kinetics, can therefore not definitely be deduced from our study. Furthermore, depending on whether benzimidazoles are given to treat intestinal or systemic parasites, a decrease in systemic bioavailability might even be considered an advantage, if intestinal drug levels were increased. However, suggestions concerning therapeutic drug monitoring for the treatment of patients with HIV and echinococcus co-infection cannot yet be given, since no concentration ranges to avoid toxicity or optimize efficacy have been established.

In conclusion, our data show that benzimidazoles exposure decreases after long-term use of ritonavir, while no significant changes in pharmacokinetic profiles are observed under short-term administration. These results are important for the safe and effective administration of these substances in certain areas of the world and should be tested for their clinical significance to optimize benzimidazole efficacy when used in combination with protease inhibitors.

Conflict of interest None of the authors were subjected to any conflict of interest.

Funding This project was funded by a research grant of the Gebert Rüf Foundation, Switzerland.

Previous presentation of data The data of this project have been presented at the Annual Meeting of the American Society of Clinical Pharmacology and Toxicology 2007 in Annaheim, CA (USA).

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